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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,782	03/15/2004	Axel Ullrich	034536-1243	9104

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,782	ULLRICH ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-9* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Invention I, claims 1-6 in the reply filed on 1/23/2007 is acknowledged.

Claims 7-9 are withdrawn from prosecution as being drawn to a non-elected invention.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Figures 11-1 to 11-4 are objected to because tables and sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. Applicants are advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 C.F.R.§§1.821-1.825 will be published as part of the patent. Applicants should amend the specification to delete any Figures which consist only of nucleic acid or protein sequences which have been submitted in their entirety in computer readable format (i.e. as SEQ ID NO:'s) and should further amend the specification accordingly to reflect the replacement of the Figure by the appropriate SEQ ID NO:.

Appropriate correction is required.

Applicants are advised that figures 3-7 and 17 are of insufficient quality to convey any meaningful information. Applicants may desire to submit better copies of the figures prior to issuance of a patent.

The disclosure is objected to because of the following informalities: The specification is not consistent with the application data sheet: the status of the related applications to which reference is made at page 1§1 of the specification should be updated. Appropriate correction is required.

The Abstract of the Disclosure is objected to because it is two paragraphs long. The abstract should be only a single paragraph of 150 words or less. Correction is required. See M.P.E.P. § 608.01(b).

Claim Interpretation

It is noted that the recitation in claims 5 and 6 of "cell line" is taken to indicate an *in vitro* cell population, and not to read on an animal or human.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,851,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-4 would be anticipated by the patented claims, as the claims are related as sub-genus to genus. With respect to claims 5 and 6, the person of ordinary skill in the art would immediately grasp, upon reading the patented claims, the desirability of making a cell line as currently claimed to

produce the viral particles used in the patented pharmaceutical compositions. Accordingly, the claims are obvious over the patented claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. § 103 as being unpatentable over Lemischka, U.S. Patent Number 5,185,438, Matthews et al. (PNAS 88:9026) and Terman et al. (BBRC

187:1579), in view of Ullrich et al. (Cell 61:203), and Ueno et al., (Science 252:844, Ueno-1 and JBC 267:1470, Ueno-2), all references cited by applicants.

Lemischka discloses DNA encoding *flk-1* and vectors comprising such (see Figures 2a-2g). At column 6, it is indicated that the invention includes soluble forms of the flk-1 receptor, as well as vectors encoding such. Retroviral vectors are specifically mentioned at column 9 line 67.

Matthews et al. disclose a recombinant vector comprising cDNA which encodes Flk-1 (See Figure 1). In the abstract, Matthews et al. disclose that *Flk-1* has strong homology to the c-Kit subfamily of receptor kinases, and in particular to the *Flt* gene product.

Terman et al. (BBRC 187:1579) disclose cDNA encoding a receptor called KDR, and conclude on the basis of sequence similarity that KDR and Flk-1 are human and murine homologues of the same receptor, respectively (see page 1582, 2nd paragraph). Terman et al. further disclose that KDR encodes a receptor for VEGF, "an endothelial cell mitogen which stimulates angiogenesis" (see abstract). At page 1584, Terman et al. state that KDR is a type III receptor tyrosine kinase, and that the similarities between KDR and *flt*, another receptor, are "reminiscent of those between the α and β chains of the PDGF receptor." In the final paragraph, on page 1585, they conclude:

> "It will be of interest to determine whether there are further similarities between the VEGF and PDGF systems." They continue, "A recently discovered endothelial cell growth factor, PlGF is structurally related to VEGF in a manner reminiscent of the similarities between the A and B forms of PDGF. It is not known whether KDR and *flt* can form functionally active dimers analogous to the PDGF receptor dimers, $\alpha\alpha$, $\beta\beta$ and $\alpha\beta$. However, the existence of structural variants of growth factors and/or receptors may possibly explain multiple cellular responses to VEGF. For example, it is not known whether KDR, *flt*, or a heterodimer KDR/*flt* mediates mitogenic activity and/or vascular permeability."

Thus, the three primary references teach that Flk-1 is a VEGF receptor falling into the class of type III tyrosine kinase receptors, with strong homology to the c-Kit family of receptors. Also taught is the insertion of Flk-1-encoding DNA into vectors, including retroviral vectors.

None of Lemischka, Matthews et al. or Terman teach or suggest construction of a recombinant vector encoding a truncated form of the disclosed *Flk-1* meeting the limitations of the claims (e.g. encoding amino acids 1-806 or other variant having extracellular and transmembrane domains but being signaling incompetent).

Ullrich et al. (Cell 61:203) disclose that "Receptor oligomerization is a universal phenomenon among growth factor receptors" (page 203, second column). At page 206, Ullrich et al. discuss various experiments in which alterations were made to the protein kinase domain of receptors, including the deletion thereof. They state that "While the kinase activity of the various receptors was dispensable for their expression and targeting to the cell surface, it was indispensable for signal transduction and induction of both early and delayed cellular responses, including mitogenesis and transformation. Although normal in its binding characteristics, the kinase-negative mutant of the EGF receptor was unable to stimulate calcium influx, inositol phosphate formation, Na+/H+ exchange, ..." , continuing "This suggests that all receptor tyrosine kinase signaling activities depend on a functional tyrosine kinase...". Thus, Ullrich et al. disclose that an EGF receptor lacking a functional kinase domain was signaling incompetent.

The remaining cited references are all drawn to examples in which tyrosine kinase receptors structurally related to the Flk-1 receptor were altered within the cytoplasmic domain, resulting in proteins that formed signaling incompetent dimers, with dominant-negative characteristics.

Ueno-1 disclose PDGFβ receptor (a subclass III tyrosine kinase receptor) lacking most of its cytoplasmic domain (but retaining extracellular and transmembrane regions). The abstract of the article clearly states "a truncated receptor can inactivate wild-type receptor function by forming ligand-dependent receptor complexes (probably heterodimers) that are incapable of mediating the early steps of signal transduction." Although the exact nature of the truncation of the receptor was not disclosed, it is described at page 845, first column as lacking most of its cytoplasmic domain, but still being capable of binding PDGF. The concluding lines of the paper state "We have observed ligand-induced formation of inactive receptor complexes between wild-type receptor and mutant receptor. These complexes appear to be incapable of autophosphorylation and signal transduction."

Ueno-2 disclose a truncated form of Fibroblast Growth Factor Receptor 1 (FGFR) lacking most of its cytoplasmic domain formed complexes with wild type FGFR, consistent with the hypothesis that the truncated FGFR interacted with wild type receptor to form nonfunctional heterodimers, thus eliminating the signaling by the wild-type FGFRs (see abstract). The truncated FGFR used by Ueno-2 consisted of the entire extracellular and transmembrane domains, and 8 amino acids of the cytoplasmic region (page 1471, first column). The final sentence of the paper suggests that inhibition of receptor function by co-expression of truncated FGFR can be used to block the actions of FGFR *in vivo*.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the nucleic acids and recombinant vectors of Matthews et al., Terman et al. or Lemischka to delete all or a portion of the sequence encoding the intracellular domain as taught by Ullrich and Ueno. The person of ordinary skill in the art would have been motivated to make such modifications in view of the teachings of Terman et al., specifically that Flk-1 is the murine homologue of the KDR receptor disclosed by Terman et al., and that it would be desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF (see teachings of Terman et al. as discussed above), and would further have been motivated by the teachings of Ullrich and Ueno that such deletions result in signaling incompetent receptors that act in a dominant-negative fashion *in vivo*, and that such results are expected to be generally applicable to tyrosine kinase receptors. The teachings of the secondary references would have provided further incentive to make such derivatives for the purpose of inhibiting the biological function of the receptor *in vivo*, which function was taught by Terman as being involved in angiogenesis. It would further have been obvious to incorporate such truncated coding sequences in a retroviral vector (and cell line containing such and producing infectious particles) because retroviral vectors are known in the art to be useful for the efficient vectors for the introduction of DNA into eukaryotic cells. With respect to the specific limitations in the claims as to termination of the coding sequence at the portion encoding amino acid 806, as this particular location falls within the cytoplasmic domain but results in the exclusion of the tyrosine kinase portion of the molecule, it is deemed to be *prima facie* obvious especially in view

of the teachings of Ullrich and Ueno that teach toward deleting the tyrosine kinase domain of the receptors.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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